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(51) International Patent Classification 6 : C12N 15/12, A61K 39/00, 35/14, C07K 14/705	A1	(11) International Publication Number: WO 96/26271 (43) International Publication Date: 29 August 1996 (29.08.96)
(21) International Application Number: PCT/US96/02156 (22) International Filing Date: 13 February 1996 (13.02.96) (30) Priority Data: 08/396,385 22 February 1995 (22.02.95) US (71) Applicants: THERION BIOLOGICS CORPORATION [US/US]; 76 Rogers Street, Cambridge, MA 02142 (US). UNITED STATES GOVERNEMENT, represented by THE DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; Office of Technology Transfer, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852-3804 (US). (72) Inventors: SCHLOM, Jeffrey; 10301 Sorrel Avenue, Potomac, MD 20854 (US). PANICALI, Dennis; 114 Nonset Path, Acton, MA 01720 (US). TSANG, Kwong, Y.; 5420 York Lane, Bethesda, MD 20814 (US). (74) Agents: BRONSTEIN, Sewall, P. et al.; Dike, Bronstein, Roberts & Cushman, 130 Water Street, Boston, MA 02109 (US).		(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: GENERATION OF HUMAN CYTOTOXIC T-CELLS SPECIFIC FOR CARCINOMA SELF-ASSOCIATED ANTIGENS AND USES THEREOF		
(57) Abstract We have discovered that by using a recombinant DNA viral vector, preferably a pox virus vector having at least one insertion site containing a DNA segment encoding the carcinoma self-associated antigen, or a cytotoxic T-cell eliciting epitope thereof, operablylinked to a promoter capable of expression in the host, human cytotoxic T-cells specific for the carcinoma self-associated antigens can be produced. The method preferably comprises introducing a sufficient amount of the recombinant pox virus vector into a host to stimulate production of cytotoxic T-cells, and contacting the host with additional antigen at periodic intervals thereafter. The additional antigen may be added by using a second pox virus vector from a different pox genus. In another embodiment, additional antigen is added by contacting the host with antigen. The antigen may be formulated with an adjuvant or in a liposomal formulation. The T-cells can be isolated. The number of T-cells can be expanded by contacting the isolated cytotoxic T-cells alternately with the carcinoma self-associated antigen or an epitope thereof and IL-2. The isolated T-cells can be used in a method for treating a host having a tumor expressing a carcinoma self-associated antigen comprising introducing cytotoxic T-cells specific for the antigen to the host and at at least one periodic interval thereafter introducing to the host a T-cell eliciting epitope of the carcinoma self-associated antigen.		

Figure 1A

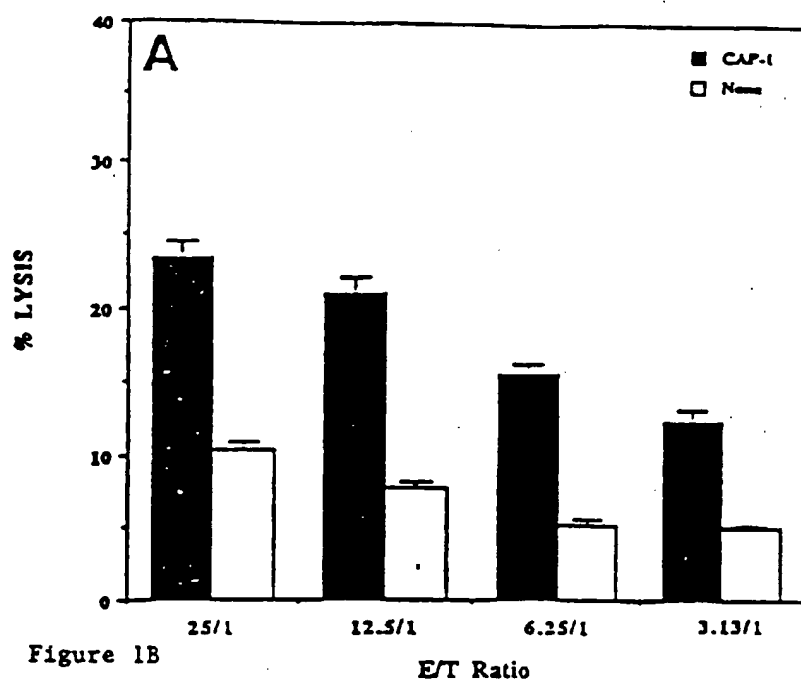


Figure 1B

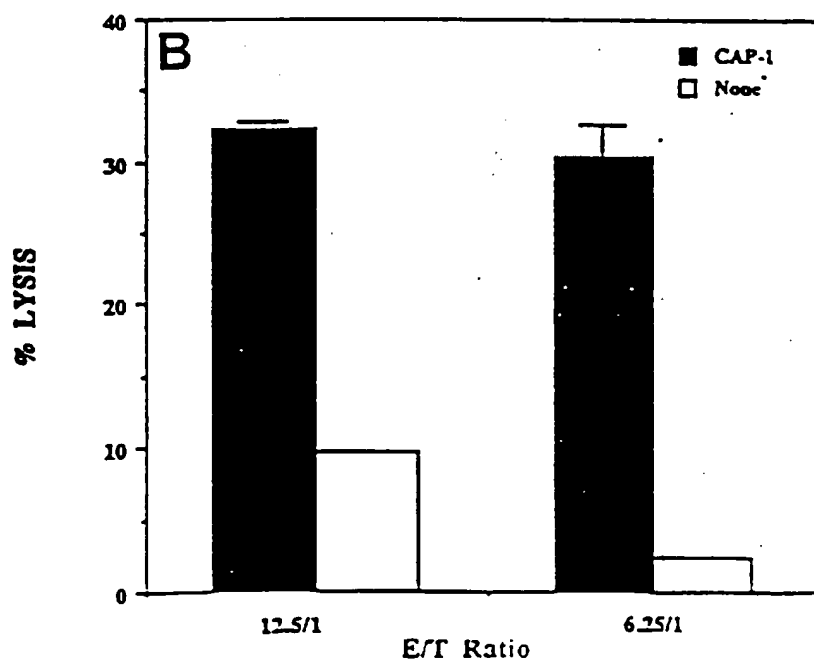
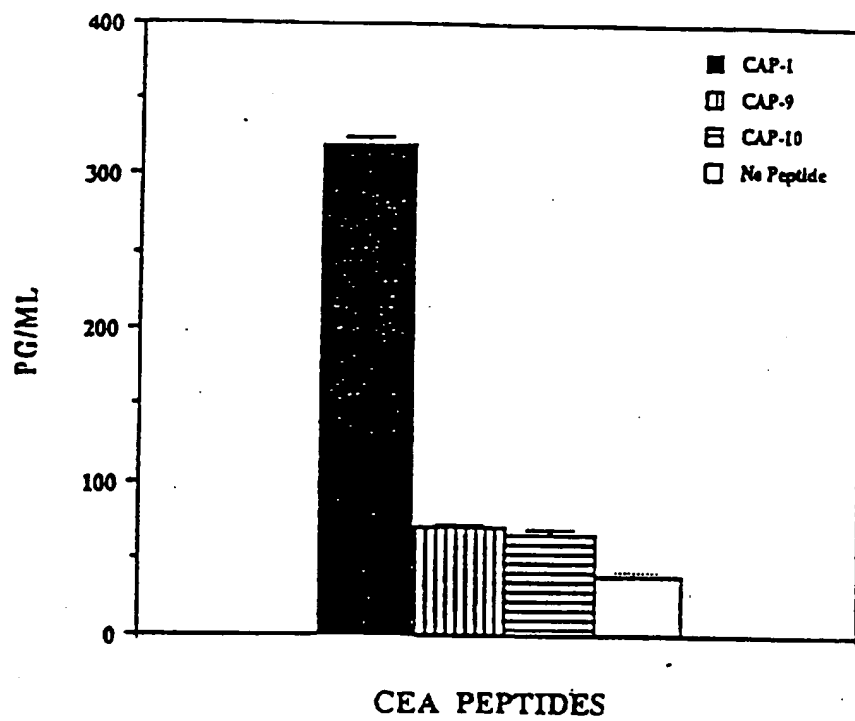


Figure 2



INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/US 96/02156

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C12N15/12 A61K39/00 A61K35/14 C07K14/705

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF THE NATIONAL CANCER INSTITUTE, vol. 84, 1992, pages 1084-1091, XP000577052 KANTOR ET AL: "ANTITUMOR ACTIVITY AND IMMUNE RESPONSES INDUCED BY A RECOMBINANT CARCINOEMBRYONIC ANTIGEN-VACCINIA VIRUS VACCINE" cited in the application see page 1084, abstract; page 1086, last paragraph-page 1087, first paragraph --- -/--	1-3, 6, 7, 10-18, 21-25, 28-31

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

2 August 1996

Date of mailing of the international search report

07. 08. 96

Name and mailing address of the ISA

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Authorized officer

Sitch, W

INTERNATIONAL SEARCH REPORT

International Application No

PL 1/US 96/02156

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>CANCER RESEARCH, vol. 52, 1992, pages 6917-6925, XP002009982 KANTOR ET AL: "IMMUNOGENICITY AND SAFETY OF A RECOMBINANT VACCINIA VIRUS VACCINE EXPRESSING THE CARCINOEMBRYONIC ANTIGEN GENE IN A NONHUMAN PRIMATE" cited in the application see page 6917,abstract;page 6920,paragraph 2;page 6921,paragraph 2-page 6922,paragraph 1</p> <p>---</p>	<p>1-3,6,7, 10-18, 21-25, 28-31</p>
X	<p>WO,A,92 19266 (US ARMY) 12 November 1992</p> <p>see page 3, line 8 - line 28 see page 8, line 34 - page 11, line 21</p> <p>---</p>	<p>1-3,6,7, 10-18, 21-25, 28-31</p>
X	<p>AIDS RESEARCH AND HUMAN RETROVIRUSES, vol. 10, no. S1, 1994, page S58 XP002009983 SCHLOM ET AL: "RECOMBINANT VACCINES FOR THE ACTIVE SPECIFIC IMMUNOTHERAPY OF HUMAN CANCER" see abstract</p> <p>---</p>	<p>1-3,6,7, 10-18, 21-25, 28-31</p>
X	<p>EP,A,0 343 946 (HOPE CITY) 29 November 1989 see page 5, line 44 - line 47; tables 1,2 see page 6, line 44 - line 45</p> <p>---</p>	<p>34</p>
X	<p>EP,A,0 263 933 (MOLECULAR DIAGNOSTICS INC) 20 April 1988 see claims 1,2,7</p> <p>---</p>	<p>34</p>
A	<p>CANCER RESEARCH, vol. 53, 1 May 1993, pages 2154-2161, XP002009984 SALGALLER ET AL: "BACULOVIRUS RECOMBINANTS EXPRESSING THE HUMAN CARCINOEMBRYONIC ANTIGEN GENE" cited in the application</p> <p>---</p>	
A	<p>NATURE, vol. 351, 23 May 1991, pages 290-296, XP002009985 FALK ET AL: "ALLELE-SPECIFIC MOTIFS REVEALED BY SEQUENCING OF SELF-PEPTIDES ELUTED FROM MHC MOLECULES" cited in the application</p> <p>---</p>	

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INTERNATIONAL SEARCH REPORT

International Application No
 PCT/US 96/02156

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	BREAST CANCER RESEARCH AND TREATMENT, vol. 38, no. 1, 1996, pages 27-39, XP000578043 SCHLOM ET AL: "STRATEGIES FOR THE DEVELOPMENT OF RECOMBINANT VACCINES FOR THE IMMUNOTHERAPY OF BREAST CANCER" see the whole document ---	1-3,6,7, 10-18, 21-25, 28-31
P,X	JOURNAL OF THE NATIONAL CANCER INSTITUTE, vol. 87, no. 13, 5 July 1995, pages 982-990, XP000567117 TSANG ET AL: "GENERATION OF HUMAN CYTOTOXIC T CELLS SPECIFIC FOR HUMAN CARCINOEMBRYONIC ANTIGEN EPITOPES FROM PATIENTS IMMUNIZED WITH RECOMBINANT VACCINIA-CEA VACCINE" see the whole document ---	1-34
P,X	PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 36, March 1995, page 249 XP002009986 TSANG ET AL: "A RECOMBINANT CEA-VACCINIA VACCINE INDUCES A CEA-SPECIFIC CYTOTOXIC T-CELL RESPONSE IN CARCINOMA PATIENTS" see abstract 1483 ---	1-3,6,7, 10-18, 21-25, 28-31
P,X	JOURNAL OF THE NATIONAL CANCER INSTITUTE, vol. 87, no. 13, 5 July 1995, pages 949-951, XP000566533 MITCHELL: "T-CELL-MEDIATED IMMUNITY TO CARCINOEMBRYONIC ANTIGEN IN HUMANS:AN EXAMPLE OF 'SWIMMING UPSTREAM'?" see the whole document ---	1-3,6,7, 10-18, 21-25, 28-31
E	WO,A,96 14074 (UNIV CALIFORNIA) 17 May 1996 see page 1, line 16 - line 23 see page 31, line 10 - line 19 see page 33, line 4 - page 34, line 10 see page 41, line 8 - page 42, line 13 see page 49, line 27 - page 51, line 27 see page 56, line 1 - page 58, line 2 -----	14,18, 21,23,25

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US96/02156

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-10, 14-20, 28-33 are directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound /composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC 1/US 96/02156

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9219266	12-11-92	AU-B- 2006092 CA-A- 2102623 EP-A- 0584266 JP-T- 6508025	21-12-92 07-11-92 02-03-94 14-09-94
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EP-A-0263933	20-04-88	AU-B- 598573 AU-B- 7686887 DE-D- 3787864 DE-T- 3787864 ES-T- 2059330 IE-B- 60279 US-A- 5231009 US-A- 5274087 JP-A- 63119681 US-A- 5122599 ZA-A- 8705951	28-06-90 24-03-88 25-11-93 10-02-94 16-11-94 29-06-94 27-07-93 28-12-93 24-05-88 16-06-92 19-02-88
WO-A-9614074	17-05-96	AU-B- 4198196	31-05-96